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PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES -
LABORATORY STUDIES

FINAL REPORT

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<p>1. During the six years covered by this report, influenza has been present in every year: influenza A/H3N2 in four years, influenza A/H1N1 in three years, influenza B in five years. In one year all three types of virus were present.</p> <p>2. HI antibody response of recruits (primary vaccination) was in general excellent to A/H3N2 and A/H1N1 and less satisfactory to influenza B. The response of the revaccinated permanent party was considerably less satisfactory.</p> <p>3. During A/H3N2 outbreaks, influenza cases were essentially eliminated in the recruit population, and very few occurred in the permanent party. Less satisfactory protection was observed with influenza B. However, attack rates did not reach 2% in either the permanent party or students.</p>			
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4. The protective antibody titers appeared to be ≥ 32 to influenza A/H3N2 and to influenza B. With influenza A/H1N1 the cutoff was less sharp, and a few cases occurred in individuals with titers > 32 .
5. The temperatures of patients reporting with the three influenza types were different. With influenza B, the temperatures were lowest; 43% of patients had temperatures between 99° and 99.8°F .
6. Inapparent infection was common, particularly with influenza B and with the A/H1N1.
7. With both influenza A and influenza B there was a gradual falloff of HI antibody titer over a six month period. When the post-vaccination titers were extremely high, this did not seriously affect the protection at six months. However, with influenza B, when initial titers were lower, it appeared that by the time six months had passed, protective efficacy would be considerably diminished.
8. Comparison of diagnostic procedures. Three diagnostic methods, namely virus isolation, HI antibody and CF tests showed much variability from year to year. It appeared important to use all three in order to avoid missing cases of influenza.
9. In one-half or more of the patients with febrile URIs, the etiology could not be determined. Parainfluenza 1 was responsible for 21 cases in 1987-88.
10. Adenovirus infections continued to be extremely rare.
11. Streptococcal pharyngitis appeared to occur in roughly 15% of the patients. In the spring of 1988 mucoid type 18 group A streptococci were cultured from eight patients. A single case of rheumatic fever was diagnosed at Fitzsimons Army Hospital in an Air Force student.
12. In recruits who were 100% vaccinated at Lackland Air Force Base, influenza seemed well controlled. Attack rates never exceeded 2%. The permanent party was also well protected, but the lack of a denominator made it impossible to calculate an accurate rate.
13. The policy of vaccinating all the students on arrival at Lackland Air Force Base has been highly rewarding. Revaccination of all permanent party seems to be worthwhile.
14. The timing of vaccination should be planned to cover the period from November through March. This is best done by vaccinating during the last half of October. Persons who have received vaccine before September should be revaccinated at the time vaccine is given to the permanent party on the Base.

FOREWORD

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

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INTRODUCTION

The investigations conducted during the period of this contract, from 1 May 1982 to 30 September 1988, were a continuation of similar studies which began at Lowry Air Force Base in 1952. The overall purpose has been the control of febrile respiratory disease in the Armed Services, particularly in the recruit population. Most of the problems encountered here have been caused by influenza viruses and adenoviruses. Adenoviruses have been virtually eliminated from the Air Force population at Lowry Air Force Base since the administration of live oral vaccine containing Types 4 and 7. This has been given to recruits soon after arrival at Lackland Air Force Base since 1973. While occasional cases have been detected each winter, the numbers have been so small that the impact of adenovirus disease is no longer considered important by the Air Force. Adenovirus vaccination was discontinued in the fall of 1987. Influenza, however, has continued to occur at the Base with one or another subtype of influenza A or influenza B or both occurring each winter. While the situation has been highly satisfactory for the past few years, questions raised by antigenic drift and antigenic shift continue to cloud the future.

METHODS

Lowry Air Force Base is a technical training base situated at the east end of Denver approximately three miles from the Medical School. The Base population is divided into two groups: 1) the students, who represent a young population which has gone through six weeks of basic training at Lackland Air Force Base in San Antonio, Texas, and then transferred for further training at Lowry Air Force Base in courses which last from a few weeks to several months; 2) the permanent party, which is made up of individuals who have been in the Air Force for a year or more and who have all previously received influenza vaccine. Approximately two-thirds are under 27 years of age and one-third are older than 27.

A secretary, Viola deTuerk, has been stationed at Lowry Air Force Base since 1952 to maintain an office in which records are kept and specimens are collected for laboratory tests. All personnel at the Base, students or permanent party who come to the Clinic with respiratory symptoms and temperatures $\geq 99^{\circ}\text{F}$, are asked to report to this office. On a voluntary basis, these individuals are asked to provide throat washing specimens and acute sera. This program is integrated with the Air Force program "Operation Gargle." A second blood specimen is obtained three weeks after the first. Compliance has, in general, been excellent. The numbers of persons reporting to the Clinic are recorded and charts are examined to obtain relevant clinical data. Lowry Air Force Base has had no hospital since the early 1960s. Patients who need hospitalization are referred to nearby Fitzsimons Army Hospital.

The throat washings (VIB) are immediately frozen at -10°C and delivered to the University laboratory two or three times per week. Throat washings are routinely tested in primary rhesus monkey kidney tissue culture. The tissue culture tubes are held for at least two weeks and are tested for hemadsorption with guinea pig cells. Those which are positive by hemadsorption are identified with CDC antisera as influenza A or B and within the A group by H.I. tests as H3N2 or H1N1. The blood specimens are refrigerated at 4°C . Acute and convalescent sera are always run in the same test. All serum pairs are run in H.I. and complement-fixation tests for influenza A and B and also for adenovirus.

The Base population has dropped somewhat in recent years. In 1988 there were between 2,800 and 3,200 students; the permanent party numbered between 4,500 and 5,000.

EPIDEMIOLOGY OF INFLUENZA

Virus Types

Influenza of some type has been present on the Base every year for the past 18 years. The number of cases at Lowry Air Force Base during the period from 1982 to 1988 is shown in Table 1.

Along with the cases at Lowry Air Force Base, there have been simultaneous outbreaks of rather small magnitude in the civilian population in the area. Influenza A H1N1 remains confined to people who were born after 1950. Influenza B has tended to occur in an endemic pattern with sharp outbreaks occurring in 1983-84 and 1985-86. The latter outbreak was of interest in that students as well as permanent party appeared to be affected in considerable numbers. Nonetheless, these numbers are extremely small in relation to the population at risk. Attack rates have never reached 2% in any year.

In the student population, nowhere is the attack rate of febrile URIs as low as with influenza A/H3N2 virus. While this virus has caused considerable amounts of illness in the civilian population and some devastating outbreaks in elderly nursing home residents, the student population has been essentially spared. The occurrence of cases of influenza A/H3N2 in the permanent party over a period of several weeks provides evidence that the student group was challenged during this period. This high degree of protection is presumably due to the fact that 100% are vaccinated and more than 84% of the students each year have had antibody titers of >32 .

Attack Rates by Squadron

Even when there were cases of influenza in the recruit population, there were no concentrations in any particular unit. In most years small numbers of cases were distributed in each of the 10 student squadrons. This was consistent with the fact that the population was highly immune and the herd effect reduced the risk of transmission by promptly terminating each infection chain.

Age Distribution of Patients with Influenza (Table 2)

The age of the individuals who became ill has been emphasized since 1977 when it appeared that H1N1 virus rarely caused illness in anyone who had been born before 1950-1953. The explanation of this observation was that individuals had their primary infection with an A/H1N1 virus before the mid 1950s followed probably by a second infection and possibly even a third, causing them to develop an antigenic imprint from the experience and a lasting immunity. These persons were immune even though many had no H.I. antibody demonstrable in their sera.

We have noted that permanent party individuals who did not have antibody to A/H1N1 in 1977, during the next 6-7 years almost all had acquired H.I. antibody presumably as a result of infections which were usually inapparent.

Thanks to the assistance of Col. Hutchison, it was possible to obtain a breakdown of the age distribution of permanent party on the Base in 1985 and following years. When A/H3N2 occurred in 1985, the highest attack rate was in individuals who were between 33 and 37 years of age. The highest attack rates of influenza B occurred in the 28-32 age group. These are rather puzzling observations and are probably best explained by the fact that these individuals are old enough to have children in school and consequently may be heavily exposed to infected children who bring the disease home.

Severity of Illness

It is generally believed that the A/H3N2 virus causes more severe illness and is associated with more complications and deaths in the civilian population than the other two viruses. Since the hospital was closed at Lowry Air Force Base during the 1960s, we have had no criteria for measuring severity or duration of illness other than the oral temperatures at the time of reporting to clinic with acute illness. These are recorded on almost all patients; results are tallied in Table 3. The distribution of temperatures was highest with H3N2 and A/H1N1, with influenza B trailing considerably. 46% of the individuals with A/H3N2 had fevers higher than 101° compared to 39% with A/H1N1 and 20% with influenza B. At the other end of the scale, 43% of individuals with influenza B had temperatures less than 100° compared to 40% with A/H1N1 and only 22% with A/H3N2. Furthermore, the number of persons with afebrile URIs was always greater than the number of cases of confirmed influenza, particularly during influenza B and A/H1N1 outbreaks.

Inapparent Infection

In several years there was clearcut evidence that infection was far more widespread on the Base than was indicated by the number of patients with febrile URIs. First, during all epidemics of influenza there has been a sharp upswing in the number of visits to the Clinic for respiratory diseases without fever. These sometimes outnumbered the patients reporting with febrile URIs by a margin of 4 to 10-fold. The peaks of these outbreaks almost always coincided with the peaks of the cases of confirmed influenza. Second, when

after the epidemic has passed, sera were collected from patients during routine visits to the Clinic for reasons other than respiratory illnesses, a considerable number of individuals showed elevated C.F. titers, indicating that they had been infected during the recent past (2-3 months). This was particularly true when influenza B was occurring.

It thus appears that influenza occurred in four forms: 1) typical clinical illness with fever; 2) influenza-like disease without fever; 3) an illness so mild that the victim did not go to the Clinic; and 4) totally inapparent infection with no symptoms.

The situation with influenza A/H3N2 and B was quite different in that the younger individuals had lower rates of illness than individuals in the 33-37 age range who tended to have the highest rates.

The Hoskins Hypothesis

There has been a good deal of interest in a series of papers published by Hoskins et al. in England describing a series of outbreaks of influenza A/H3N2 in a boys' school in the London area between 1972 and 1976. Hoskins concluded that the usefulness of annual revaccination is very questionable. He claims that in the boys' school all that was gained by annual vaccination was to delay the illness by one year. That is, boys who were protected by vaccine the first year gained nothing in terms of protection when the outbreak came the following year or when a new virus appeared.

At Lowry Air Force Base we are unable to confirm this phenomenon. If this situation were applied here, we should encounter most of our illness in younger segments of the permanent party, since there are large numbers of individuals in that group who were vaccinated as students and who stayed on as permanent Air Force personnel and were revaccinated each year. Among the many individuals on the Base between the ages of 18 and 22, we would expect to see many cases of influenza when A/H3N2 was prevalent. This we have not seen. The explanation for this difference is not yet clear.

VACCINE

Composition

The vaccines used throughout this period were trivalent preparations of inactivated allantoic fluid containing A/H3N2, A/H1N1 and influenza B viruses. Each of the components consisted of 15 mcg of hemagglutinin of the virus. The strain composition of the virus varied from year to year, changes being made to accommodate for antigenic drift.

The composition of the vaccines is shown in Table 4. Before 1986 the vaccines were prepared by the Connaught Laboratories as whole virus preparations, but from 1986 on ether-split vaccines prepared by Parke-Davis were used. This change was made as a result of a study done collaboratively

with Col. Gremillion at Lackland Air Force Base. Blood specimens were collected before and after vaccination from 100 recruits who had received whole virus vaccine and another 100 who had received ether-treated vaccine. The H.I. antibody response was almost identical in the two groups. Since that time the ether-treated vaccine has been used. The ether-split preparations are believed to cause fewer reactions. However, reactions to whole virus vaccine have not been a problem in the Air Force recruits. There are reasons to question whether the ether-treated vaccines provide as solid an immunity as whole virus vaccines but the results have been very satisfactory in recruits.

Antibody Response

The antibody responses of recruits and permanent party are presented separately. The reason for this is that in the recruit population, the response to primary vaccination is uniformly far better than that to revaccination in the permanent party. The responses of an elderly population in an Air Force retirement home in San Antonio are also presented. These were tested at the request of Major Martin Evans at Lackland Air Force Base, who was interested in observing the impact of influenza in an elderly population.

Response in Recruits (1986)

With both influenza A/H3N2 and influenza A/H1N1, the sera were tested against both the vaccine strain and the epidemic strain which came along the next year. The vaccine contained A/Mississippi/85, A/Chile/83 and B/Ann Arbor/86. With A/Mississippi/85, the percent of persons with titers ≤ 8 fell from 27% to 0% after vaccination, and the percent with titers ≥ 32 rose from 44% to 99%. With A/Chile/83 the percent of individuals with prevaccination titers ≤ 8 fell from 24% to 1%. The percent with titers ≥ 32 rose from 30% to 100%. With the B/Ann Arbor/86 strain, the percent with prevaccination titers ≤ 8 fell from 47% to 1% after vaccination. The percent with titers ≥ 32 rose from 19% to 88%. These highly satisfactory figures are comparable to those found in students at Lowry Air Force Base throughout this period. Coverage has been 100%. We have found no unvaccinated Air Force students during the last six years, a tribute to the thoroughness of the procedures carried out at Lackland Air Force Base.

Antigenic Drift - A/Taiwan/86

The response of students to the heterologous A/Leningrad/86 strain which drifted only slightly from A/Mississippi/85 was quite satisfactory. However, a very different situation was found with A/Taiwan/86 which differed markedly from the vaccine strain A/Chile/83. The response to A/Taiwan/86 is therefore of considerable interest. 31% had titers ≤ 8 in their prevaccination sera and only 4% in the postvaccination sera. The percent of persons with titers ≥ 32 rose from 1% to 79%.

We meanwhile obtained quite different results at Lowry Air Force Base. We had noted that only 45% of post-vaccination students who had received

vaccine containing A/Chile/83 had titers of ≥ 32 . We had obtained a small amount of monovalent A/Taiwan/86 vaccine and had vaccinated 40 recruits at Lowry Air Force Base in October and had obtained pre- and post-vaccination sera. The monovalent booster produced highly satisfactory results. The percentage of individuals with titers ≥ 32 rose from 45% to 100%.

We attribute the difference to the fact that A/H1N1 influenza presumably was prevalent at Lackland Air Force Base when vaccine was given and that a number of individuals must have been infected during the period between the collection of pre- and post-vaccination sera.

Response in Permanent Party (Table 7)

In general, individuals with titers ≤ 8 before vaccination were considerably fewer than among the recruits. However, the response to the vaccine was also less impressive and the post-vaccination distribution of titers favored the recruits over the permanent party. The percent of individuals with titers ≥ 32 is considerably lower when tested with B/Ann Arbor/86 and with the heterologous viruses A/Leningrad/86 and B/Taiwan/86.

Response of Air Force Retirement Center Residents (Table 8)

Residents of the Air Force Retirement Center followed the same pattern as the permanent party. Most individuals had been vaccinated previously with trivalent vaccine. The response to A/Chile/83 was not as good as that in the permanent party nor was the response to B/Ann Arbor. The response to heterologous viruses of A/Taiwan was slightly inferior to that of the permanent party.

DURATION OF IMMUNITY

Influenza A

HI antibody titer following vaccination usually peaks between two and four weeks after the administration of aqueous vaccine and then falls off gradually over a period of many months. In recruits and permanent party who were seen in the clinic with diseases other than influenza at varying periods after they had received vaccine, a gradual fall of HI antibody titer was observed (Table 9). With influenza A the initial titers were very high with 97% of individuals having titers ≥ 32 during the first and second months after vaccination.

After the first six months or more only 76% had titers ≥ 32 . We also observed that by the end of the year, the titer dropped further so that only half as many individuals had titers in the protective range as during the month or two after vaccine administration. It is on this basis that annual revaccination is regarded as important.

Influenza B

With influenza B the situation is more troublesome because the percent of individuals who have received recent vaccines with high titers tend to be lower. In Table 10 the levels of antibody following vaccination with B/Singapore/79 are shown. One to two months after vaccination only 59% of individuals had titers ≥ 32 . By six months or more this percent was down to 28%. That this may have some significance was suggested by the experience of 1985-86 when influenza B was prevalent throughout January at a low level of only one or two cases a week and then developed into a sharp epidemic with 78 cases in the permanent party and 48 cases in the students.

These data suggest that vaccine should not be given too early in the fall if one is to expect a high level of protection when the disease occurs late. For example, some six months after vaccine is given, individuals who are vaccinated earlier probably need revaccination in the fall.

PROTECTIVE ANTIBODY LEVELS

A/H3N2

During this period we had several appearances of influenza A virus of the H3N2 subtype. Abundant evidence collected in the past indicated that HI titer of ≥ 32 is protective. This holds when the HI tests are done with the epidemic strain, and when the strain is of sufficient avidity to detect antibody in small amounts. Almost all student vaccinees have titers of ≥ 2 . This has been true also of the permanent party. The heterologous response to the new strain which came along the next year has also been routinely measured. In general, the response has been adequate to provide protection against the new strains.

A/H1N1

The homologous response to the A/H1N1 component of the vaccine has been highly satisfactory. In most years from 93% to 100% of the recipients have had post-vaccination titers of ≥ 32 .

The heterologous response has been somewhat different. The main shift in this virus occurred in 1987-88 when the A/Taiwan/86 strain of A/H1N1 appeared. The A/Chile/83 virus had been the H1N1 component for three years and produced an excellent response to the homologous virus but a very poor one for A/Taiwan/86. For that reason monovalent A/Taiwan/86 vaccine was used to supplement the trivalent vaccine.

Whole virus antigen was used rather than ether-split antigens because the latter are too nonspecific to give reliable results. The appearance of a large number of cases of influenza A/H1N1 has made it possible to estimate the protective antibody titer against these viruses. The results with A/H1N1 virus has never been as good as with A/H3N2. While there is a decline in the number of cases in individuals who have titers ≥ 32 with A/H1N1 viruses, the result is not as sharp with A/H3N2. A few individuals were found to have influenza with titers of 64 or even as high as 128.

Influenza B

The influenza B strain has been particularly difficult with the appearance of relatively nonavid influenza B viruses. Ether-split antigens have been used widely for diagnosis and also to evaluate vaccine response. The titers obtained with the ether-split antigens lack specificity and often are eight-fold higher than those obtained with whole virus antigens. In 1985-86 when a large number of influenza B cases occurred at Lowry Air Force Base, an attempt was made to demonstrate a protective level of antibody using ether-split antigens without success. When tissue culture antigens from the second T.C. passage of strains isolated from epidemic were used instead of the ether-split antigen (of the 8th egg passage), a clearcut protective effect was observed. It appears, therefore, that with a suitable antigen, the situation with influenza B is comparable to that with influenza A/H3N2, i.e., a titer ≥ 32 is protective.

LABORATORY OBSERVATIONS

Comparison of Diagnostic Methods

Each year the virus isolation and two serologic tests have been compared for confirmation of the diagnosis of influenza. All throat washings have been tested in RMK for virus isolation and all serum pairs have been run in C.F. tests and H.I. tests. In the latter we used antigens from the vaccine strain and a recently isolated epidemic strain. It is obvious when one looks at the results that there is great variability. Although in the past influenza A/H3N2 has been considered the most readily isolated, in two of the recent outbreaks the recovery rate has been relatively poor. Results in 1987-88 were the poorest, with only one virus recovered from 10 specimens tested.

With influenza A/H1N1 the results were usually poor. With influenza B viruses were isolated from 75% of throat washings in 1985.

The results of the two serologic tests varied greatly from year to year with one being better than the other in one year and vice versa the next. In general, with the HI tests, the results were better when the epidemic strain was used rather than the vaccine strain and when avid whole virus preparations were used. Complement-fixation tests have been variable in their effectiveness, but they remain useful as a backup on the other two procedures.

It is obvious that all three procedures are necessary if one is to approach the complete identification of all cases. The reliance that many people have placed on virus isolation as a "gold standard" certainly is not warranted by these observations.

The parainfluenza I information is included on the table simply to point out that the virus was not recovered from many individuals in whom the diagnosis was confirmed by rises in titer in CF tests from <8 to >16 . Sera were not carried beyond the 1:16 dilution because of expense of the antigen.

Avidity

The concept of avidity was first developed by George Hirst in the late 1940s when the "A-prime" virus was first identified. The term means that the virus (in early egg passages) does not combine adequately with antibody, giving a false low titer. This has caused trouble in the laboratory, first with A/H1N1 isolates and more recently with influenza B isolates. Table 12 provides a good example of lack of avidity. In this table the results of HI tests are presented on serum pairs from eight individuals who were proved to have influenza B both by isolation of virus and significant rises in CF antibody titers. These serum pairs were run in HI tests with seven different antigens. These antigens were:

- 1) B/USSR-W.V.
- 2) B/USSR-E.T.
- 3) B/Ann Arbor/86
- 4) B/Canada/85
- 5) B/Denver/1/86. This was isolated from a civilian who had acquired the disease in New York from a relative who had just arrived with influenza after an air trip from Bombay in India.
- 6) B/Denver/2/86
- 7) B/Denver/3/86. The strains B/Denver/2/86 and B/Denver/3/86 were isolated from patients at Lowry Air Force Base in rhesus monkey kidney tissue culture. Virus pools of the supernatant fluid had been prepared from the second tissue culture passage for use as antigen in the HI tests.

In the first two columns the difference in titer between whole virus and ether-treated B/USSR antigens is obvious. The titers with whole virus are reasonably high and seven of eight individuals had significant rises in titer. With the ether-treated antigen, acute titers were so high that only five of eight persons had fourfold rises in titer. There might have been more individuals who had significant rises in titer if the sera had been run beyond 1024.

The sera all had titers which were very high in both acute and convalescent serum in tests with the ether-treated B/USSR antigen. However, acute sera titers were very low in tests with B/Ann Arbor, B/Canada, B/Denver/1,2,3/86. Convalescent titers, however, were high, indicating a satisfactory level of avidity for B/Denver/2/86 and B/Denver/3/86.

The lack of avidity is best demonstrated in the strain B/Denver/1/86 E7, for which only four of eight individuals had titer rises of \geq fourfold. All had very low acute phase titers and failed to show antibody in their convalescent sera. The most satisfactory results were obtained with the two Denver strains in tissue culture and with B/Canada/85. With these three strains acute phase titers are reasonably low and the convalescent titers reasonably high.

Antigenic Drift

The data in Table 12 also shows the obvious antigenic drift. The differences in titer between B/USSR/83 and the two Denver strains, B/Denver/2/86 and 3/86, is evident. The B/USSR/83 whole virus had been passed 29 times in eggs

and was considerably more avid than the early egg passages. Drift is also evident in the differences in the titers observed with the immune sera provided by the CDC. The titers with the 1986 Denver viruses are considerably lower than those obtained with the homologous USSR antiserum.

SEARCH FOR OTHER CAUSES OF FEBRILE URI

Each year the etiology of 50% or more of illnesses of patients reporting to the Clinic with febrile URI remains unknown. In the past we have looked for and found small numbers of febrile URIs caused by enteroviruses or coronaviruses. These have tended to occur in small clusters of 15-20 cases. In the past we have also looked for respiratory syncytial virus by complement-fixation tests and in one year found two individuals with significant increases in titer and 11 others with twofold rises in titer. The following year we found no more cases and concluded this is probably not a significant pathogen in this population. In 1987 we looked for illness with infection by Chlamydia TWAR using psittacosis CF antigen obtained through WRAIR. A single case was detected in two years with a fourfold rise in titer. A number of twofold rises were also demonstrated. We concluded this also is probably not a significant pathogen.

In the season 1987-88 we encountered an outbreak of 21 cases of parainfluenza I infection. Nineteen of these occurred in students and two in young members of the permanent party. These viruses could be recognized by the C.P.D. which they had showed in monkey kidney tissue culture. The hemadsorption of guinea pig cells could not be inhibited by influenza antisera. They were identified in the University Hospital diagnostic laboratory by means of FA antibody tests. Complement-fixation tests on sera from these individuals showed a significant rise in titer in all but one case from which virus had been isolated and in nine additional persons from whom virus was not isolated.

There was little in the way of clinical symptoms to distinguish the illnesses from mild cases of influenza or from each other. Whether they represent in large measure a single unidentified agent or simply a mixture of many viruses is hard to state at the present time.

Adenoviruses continue to be extremely rare. The occasional appearance in individuals with CF titers as high as >32 strongly suggests that there may be some adenovirus illness occurring either at Lackland or at Lowry Air Force Base. We remain curious to see what will happen now that vaccine has been discontinued more than a year and will continue to test all persons with CF tests using adenovirus antigens.

Patients with febrile pharyngitis caused by beta hemolytic streptococci occur each year in about 15% of the individuals who come in with febrile URI each year. A cluster of mucoid type 18 streptococci in early 1987 caused some concern but this has not recurred. It is of interest that all recruits arriving from Lackland in the fall of 1988 had received an injection of bicillin because of concern about the recurrence of rheumatic fever. This situation will be carefully monitored.

PREDICTIONS OF VACCINE EFFECTIVENESS

Individuals who have worked with influenza viruses for a long time learned long ago the folly of predicting the behavior of this virus. Each year brings some surprises. Nevertheless, it is necessary each year to make decisions about the vaccines for the coming winter and to make appropriate changes in the event that the picture does not look promising. During the period of the studies at Lowry Air Force Base, sufficient data have been obtained to make some estimates on whether or not the vaccine will be effective. The behavior of these three viruses have been quite different.

A/H3N2 (Table 13)

The data on influenza A/H3N2 virus are abundant. At Lowry Air Force Base, illness caused by influenza H3N2 has been virtually eliminated in the recruit population. It appears that with 100% vaccination coverage and with 90% or more of the recruits having had HI antibody titers of ≥ 32 , febrile URIs have virtually disappeared from the recruit population. That this group was challenged by the epidemic A/H3N2 virus was clearly shown by the occurrence of a number of cases over a period of eight weeks or more in the permanent party.

To make these estimates more explicit, the recruits were divided into three groups on the basis of HI antibody titers following vaccination. Most of the cases occurred in individuals with titers of 8 or < 8 . This group has been labeled as "most susceptible." Those with titers of ≥ 32 are considered essentially "protected." Persons with titers of 16 are a swing group which has shown considerable protection but will contribute a certain number of cases. The difference in the attack rates of persons with titers of ≤ 8 and those with titers of ≥ 32 is often tenfold. Those with titers of 16 will fall somewhere in between.

We have observed during this period that when there is only minor antigenic drift (single drift), vaccine prepared from strains acquired the year before still provide protection. A year later when there is further drift (double drift), it may be necessary to change the vaccine strain. The experience with the A/H3N2 outbreak of 1985-86 illustrates this point. A/Mississippi/85 vaccine produced a good antibody response against A/Leningrad/86 despite some drift. However, when the same vaccine was tested against A/Sichuan/87 virus, antibody response was poor and presumably could not have protected as well against A/Sichuan/87.

A/H1N1 (Table 14)

With the A/H1N1 virus the situation is relatively similar. In most years the antibody response of the students to vaccination has been extraordinarily good with 90% or more having titers of ≥ 32 . Though more cases have occurred than with A/H3N2, the overall attack rate has been relatively low in the face of three distinct challenges. It was noted that when the A/Taiwan appeared in 1987 with a significant antigenic drift, the situation would have been considerably worse if monovalent A/Taiwan vaccine had not been given as a booster for the A/Chile vaccine, which was the vaccine strain for that year.

Influenza B (Table 15)

With influenza B the situation has been the least favorable. The behavior of influenza B viruses has been particularly unpredictable since 1972 when the B/Hong Kong viruses first appeared. Low avidity has been a problem in some years and in the past caused considerable difficulty in performing HI tests. The situation appeared to have improved somewhat when B/Singapore/79 appeared and response of recruits to this virus in the vaccine was remarkably good.

The low avidity of several recently isolated viruses has made it necessary to use ether-treated antigens in HI tests. With these antigens the protective titer is obviously higher than 32 and cases of influenza occur in persons with titers of 64, 128 or even higher.

With a good vaccine strain, the situation with influenza B should be comparable to that with influenza A/H3N2. Many studies in the past have indicated that influenza B vaccine may be as effective or more effective than influenza A vaccine.

RECOMMENDATIONS

Finally, there are two questions which need to be answered. The first is whether annual revaccination of all the permanent party is necessary. We have obtained specific data on this point during every outbreak. There has been obviously a higher attack rate in the unvaccinated individuals than those who received vaccine in the current year. However, because we were never sure how many people had not been vaccinated on the Base, we lack a denominator. Our best guess is that the protection provided is 60% or more, and if there are no revaccinations done each year, the attack rates in the permanent party would probably be considerably higher than they have been in recent years.

The second question is when is the best time to administer the vaccine. While the response to the vaccine is very good, as it has been recently with the influenza A strains, there may be some falloff in protection over a period of six months but this is probably not very serious. With a good influenza B vaccine, the situation should be similar. With a poor type of response like that seen this year, immune status of the vaccinated people would be considerably reduced within six months.

Influenza outbreaks have usually occurred in December or January, but we recently encountered outbreaks in November and December. It seems advisable to stay with the last part of October as the optimum period to give vaccine in order to cover a six month period and assume that there will be no epidemic later than March. This would cover a six month span. Those who are vaccinated in September or earlier probably should be revaccinated when the rest of the permanent party are vaccinated. When there is major antigenic drift, a booster of monovalent vaccine in December or January is undoubtedly helpful. When there is antigenic shift, the vaccine should be administered as soon as it is available.

Table 1

Number of confirmed cases of influenza at Lowry Air Force Base, 1982-1988

<u>Year</u>	<u>Number of persons with indicated influenza virus</u>					
	<u>A H3N2</u>		<u>A H1N1</u>		<u>B</u>	
	<u>Student</u>	<u>Perm. Party</u>	<u>Student</u>	<u>Perm. Party</u>	<u>Student</u>	<u>Perm. Party</u>
1982-83	1 (0)	8 (0)	14 (0)	6 (0)	0 (0)	11 (2)
1983-84	-	-	12 (0)	20 (0)	14 (0)	56 (13)
1984-85	4 (0)	32 (9)	-	-	0 (0)	2 (0)
1985-86	2 (0)	14 (2)	-	-	48 (1)	78 (9)
1986-87	-	-	23 (0)	98 (15)	-	-
1987-88	-	10 (0)	-	-	0	3 (0)

Note: Data in parentheses are number of illnesses in unvaccinated persons, estimated to constitute ~10%-15% of the permanent party.

Table 2

Distribution by age in permanent party of three types of influenza

	Influenza Type		
	A/H3N2	A/H1N1	B
Year	1984-85	1986-87	1985-86
No. of Persons	38	77	55
Age			
18-22	3 (0.1)	9 (0.11)	8 (0.3)
23-27	4 (0.2)	35 (1.8)	14 (0.7)
28-32	9 (0.8)	<u>22 (2.0)</u>	<u>17 (1.6)</u>
33-37	<u>15 (2.0)</u>	9 (1.2)	7 (1.0)
38-42	4 (0.8)	2 (0.4)	8 (1.6)
43-47	1 (0.7)	0 (-)	1 (0.6)
≥ 48	0 (-)	0 (-)	0 (-)

() = attack rate %

Table 3

Distribution of dispensary oral temperatures of serologically confirmed patients with H3N2, H1N1 or B influenza. All had received vaccine.

Virus	<u>Percent of Persons with Confirmed Influenza</u>		
	H3N2	H1N1	B
No. of Persons	119	58	67
Temperature			
99-99 ⁸	22	40	43
100-101 ⁸	32	21	36
101-101 ⁸	29	29	13
≥ 102	17	10	7
	46	39	20

Table 4

Changes made in vaccine to accommodate for antigenic drift

Year	Vaccine Composition		
	<u>A/H3N2</u>	<u>A/H1N1</u>	<u>B</u>
1982	A/Bangkok/1/79	A/Brazil/11/78	B/Singapore/222/79
1983	A/Philippines/2/82	A/Brazil/11/78	B/Singapore/222/79
1984	A/Philippines/2/82	A/Chile/1/83	B/USSR/100/82
1985	A/Philippines/2/82	A/Chile/1/83	B/USSR/100/82
1986	A/Mississippi/86	A/Chile/1/83	B/Ann Arbor/86
1987	A/Leningrad/100/86	A/Taiwan/86	B/Victoria/87

Table 5

Results of HI tests with serum pairs from 75 recruits at Lackland Air Force Base who received vaccine immediately on arrival at the Base. The A/Leningrad virus was tested against only 50 recruits. Bled 11/4 and 12/2/86.

Test Antigen	Serum	% <8	Cumulative % >							
			8	16	32	64	128	256	512	1024
A/Miss/85* (H3N2)	Pre	27	74	57	<u>44</u>	25	18	11	4	0
	Post	0	100	99	<u>99</u>	96	91	84	80	65
A/Leningrad/86 (X91)	Pre	30	70	34	<u>18</u>	8	0	0	0	0
	Post	4	96	94	<u>86</u>	78	70	60	34	20
A/Chile/83* (H1N1)	Pre	24	76	49	<u>30</u>	11	5	1	0	0
	Post	1	100	100	<u>100</u>	99	98	94	87	79
A/Taiwan/86 (H1N1)	Pre	81	18	2	<u>1</u>	0	0	0	0	0
	Post	4	96	92	<u>79</u>	68	51	32	17	8
B/Ann Arbor/86*	Pre	47	52	28	<u>19</u>	6	5	0	0	0
	Post	1	99	95	<u>88</u>	68	37	28	9	5

*Strain contained in the vaccine.

Table 6

Comparison of H.I. antibody titers for A/Taiwan/86, and A/Chile/83 of students before and after receiving standard trivalent vaccine and after monovalent A/Taiwan vaccine booster given 2-3 months after standard vaccine.

Test Antigen	Serum Specimen	Cumulative percent with H.I. titers >								
		<8	8	16	32	64	128	256	512	1024
A/Taiwan/86	Pre-Trivalent (40)	92	8	-	-	-	-	-	-	-
	Post-Trivalent 2-3 mo. (34)	28	72	62	45	37	32	12	10	8
	Post-Monovalent 3 wks. (34)	-	100	100	100	95	92	71	53	41
A/Chile/83	Pre-Trivalent (40)	23	77	41	24	11	3	-	-	-
	Post-Trivalent 2-3 mo. (34)	-	100	100	100	100	97	94	82	62
	Post-Monovalent 3 wks. (34)	-	100	100	100	100	100	97	94	76

Table 7

Results of HI tests with serum pairs from 75 permanent party at Lackland Air Force Base who received vaccine. The A/Leningrad virus was tested against serum from only 50 permanent party. Bled 10/6 and 11/5/86.

Test Antigen	Serum	% <8	Cumulative % >							
			8	16	32	64	128	256	512	1024
A/Miss/85* (H3N2)	Pre	0	101	94	<u>83</u>	64	47	54	33	12
	Post		99	99	<u>98</u>	90	65	49	24	13
A/Leningrad/86 (X91)	Pre	12	88	58	<u>38</u>	20	12	6	2	0
	Post	2	98	84	<u>62</u>	40	20	8	2	0
A/Chile/83* (H1N1)	Pre	1	99	96	<u>89</u>	73	48	33	25	16
	Post	1	99	99	<u>96</u>	89	64	44	29	13
A/Taiwan/86 (H1N1)	Pre	35	65	41	<u>24</u>	16	8	1	1	0
	Post	24	76	48	<u>32</u>	17	9	2	1	1
B/Ann Arbor/86*	Pre	19	81	57	<u>41</u>	24	8	7	3	0
	Post	7	93	82	<u>58</u>	38	17	9	4	1

*Strain contained in the vaccine.

Table 8

Results of HI tests of paired sera from 75 residents of the Air Force Retirement Home at Lackland Air Force Base in San Antonio. All received standard vaccine. The A/Leningrad virus was tested against serum from only 50 residents. Bled 10/15 and 11/17/86.

Test Antigen	Serum	%	Cumulative % >							
		<8	8	16	32	64	128	256	512	1024
A/Miss/85* (H3N2)	Pre	5	94	79	<u>60</u>	47	30	13	4	1
	Post	1	100	96	<u>88</u>	81	58	44	23	11
A/Leningrad/86 (X91)	Pre	22	78	50	<u>30</u>	16	6	2	0	0
	Post	8	92	80	<u>60</u>	34	22	14	6	2
A/Chile/83* (H1N1)	Pre	13	86	66	<u>41</u>	22	11	6	1	0
	Post	3	98	89	<u>64</u>	44	21	10	3	0
A/Taiwan/86 (H1N1)	Pre	44	55	26	<u>18</u>	10	3	3	2	1
	Post	31	70	35	<u>24</u>	12	5	4	1	0
B/Ann Arbor/86*	Pre	29	70	51	<u>31</u>	18	5	1	1	0
	Post	8	92	73	<u>53</u>	41	12	5	1	0

*Strain contained in the vaccine.

Table 9

Decline in HI antibody titers after vaccination in permanent party in tests with influenza A/Miss/86-87.

Time after vaccination	No. Persons	Cumulative % with HI titer of:								
		<8	8	16	32*	64	128	256	512	1024
1-2 mo.	91	1	98	98	<u>97</u>	85	65	49	27	12
3-4 mo.	47	2	99	97	<u>86</u>	73	54	48	22	9
5-6 mo.	21	5	96	96	<u>86</u>	67	38	24	10	5
> 6 mo.	30	0	99	86	<u>76</u>	56	46	19	6	3

*Titer of 32 or more is considered "protective".

Table 10

Decline in HI antibody titers after vaccination in permanent party
in tests with influenza B/Singapore/79 - 1984-85

Time after vaccination	No. Persons	Cumulative % with HI titer of:								
		<8	8	16	32*	64	128	256	512	1024
1-2 mo.	17	0	100	88	<u>59</u>	24	-	-	-	-
3-4 mo.	47	6	94	71	<u>41</u>	19	8	2	2	-
5-6 mo.	27	0	100	64	<u>44</u>	17	-	-	-	-
> 6 mo.	39	10	90	57	<u>28</u>	17	8	8	-	-

*Titer of 32 or more is considered "protective".

Table 11

Comparison of rates of virus isolation
w/results of HI and CF tests

<u>Virus</u>	<u>Year</u>	<u>No. tested</u>	<u>% Positive</u>		
			<u>Virus isolation</u>	<u>H.I.</u>	<u>C.F.</u>
A/H3N2	1980-81	16	25	75	94
	1982-83	6	100	83	67
	1984-85	31	68*	71	74
	1987-88	10	10	90	80
A/H1N1	1980-81	99	-	82	72
	1983-84	33	48	79	93
	1986-87	77	66	86	61
B	1979-80	25	48	84**	88
	1985-86	90	75	63	91
Para I***	1987-88	21	57	-	95

* With good RMK rate was 89%

** Tested with ET antigen; with WV antigen rate was 32%

*** Identified by FA test in University Hospital Laboratory

Table 12

Results of H.I. tests with paired sera from 8 patients with Influenza B
using 7 different antigens*

Patient No.	Serum	Antigen							CF Titer B/USSR/83
		B/USSR/83 E-29 W.V.	B/USSR/83 E.T. (CDC)	B/AA/86 E1	B/Can/3/85 E7	B/Den/1/86 E7	B/Den/2/86 TC2	B/Den/3/86 TC2	
1	Ac. Conv.	32 1024	128 1024	<8 64	<8 64	<8 16	8 128	8 256	<8 64
2	Ac. Conv.	16 1024	64 1024	<8 1024	<8 1024	<8 128	8 1024	<8 1024	<8 512
3	Ac. Conv.	32 512	128 1024	8 128	8 128	<8 32	8 256	<8 1024	<8 64
4	Ac. Conv.	32 256	128 1024	8 32	16 64	<8 8	16 64	16 64	8 64
5	Ac. Conv.	128 1024	512 1024	8 32	8 64	<8 16	16 256	16 1024	<8 128
6	Ac. Conv.	64 1024	512 1024	<8 16	<8 32	<8 <8	<8 128	8 1024	8 128
7	Ac. Conv.	32 64	128 256	<8 8	<8 16	<8 8	8 64	8 64	<8 32
8	Ac. Conv.	32 128	256 1024	<8 32	<8 32	<8 8	<8 64	<8 128	<8 64
Antisera									
A/Phil/82	<8	<8	<8	<8	<8	<8	<8	<8	-
A/Chile/83	<8	<8	<8	<8	<8	<8	<8	<8	-
B/USSR/84	1024	1024	1024	1024	1024	64	64	128	-
>4x rise	7/8	5/8	7/8	8/8	8/8	4/8	8/8	8/8	8/8

*All whole virus antigens except B/USSR/83-ET

Table 13

Post-vaccination titers for challenge strains of H3N2 influenza and attack rates in students from 1982 to 1988

<u>Year</u>	<u>Vaccine Virus</u>	<u>Challenge Virus</u>	<u>% with titers against challenge viruses of:</u>			<u># of cases</u>	<u>Attack Rate (%) H3N2</u>
			<u><8</u>	<u>16</u>	<u>>32</u>		
1982-3	A/Bangkok/79	A/Bangkok/79	1	5	94	1	0.05
1983-4	A/Bangkok/79	A/Bangkok/79	0	1	99	N.C.*	-
		A/Phil/82	8	12	80	N.C.*	-
1984-5	A/Phil/82	A/Phil/82	7	9	84	4	0.2
1985-6	A/Phil/82	A/Miss/85	0	11	89	2	0.1
1986-7	A/Miss/85	A/Leningrad	9	7	89	N.C.*	-
		A/Leningrad/86	1	0	99	0	0
1987-8	A/Lenin/86	A/Colorado	5	6	89	0**	0
		A/Sichuan	2	8	90	0	0

*N.C. = No challenge

** = 12 cases detected in permanent party

Table 14

Post-vaccination titers for challenge strains of H1N1 influenza and attack rates in students from 1982-1988

<u>Year</u>	<u>Vaccine Virus</u>	<u>Challenge Virus</u>	<u>% with titers against challenge viruses of:</u>			<u># of Cases</u>	<u>Attack Rate %</u>
			<u>≤8</u>	<u>16</u>	<u>≥32</u>		
1982-3	A/Brazil/79	A/Chile/83	4	4	92	14	0.5
1983-4	A/Chile/83	A/Chile/83	4	2	94	12	0.5
1984-5	A/Chile/83	A/Chile/83	2	1	87	N.C.*	-
1985-6	A/Chile/83	A/Chile/83	1	2	97	N.C.*	-
1986-7	A/Chile/83	A/Chile/83	0	0	100		
		A/Taiwan/86	38	17	45	23	0.8
1987-8	A/Taiwan/86	A/Taiwan/86	0	8	92	N.C.*	

*N.C. = No Challenge

Table 15

Post-vaccination titers for challenge strains of influenza B and attack rates in students from 1982-1988

<u>Year</u>	<u>Vaccine Virus</u>	<u>Challenge Virus</u>	% with titers against challenge viruses of:			<u># of Cases</u>	<u>Attack Rate %</u>
			<u><8</u>	<u>16</u>	<u>>32</u>		
1982-3	B/Singapore/79	B/Sing/79	0	0	100	0	0
1983-4	B/Sing/79	B/Sing/79	3	3	94	14	0.5
1984-5	B/Sing/79	B/USSR/83	24	24	52	0	0*
1985-6	B/USSR/83	B/USSR/83-ET	0	0	100**	48	1.7
		B/USSR/83-WV	64	4	32	-	-
1986-7	B/USSR/83	B/AA/86	8	19	73	N.C.***	-
1987-8	B/AA/86	B/Victoria/87	3	3	94	0	0

* 2 cases of influenza B were detected in April and May

** Titer with E.T. antigen. All others were tested with W.V. antigen.

***No Challenge